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# Improving the Efficacy of Reduced Intensity Allogeneic Transplantation for Lymphoma using Radioimmunotherapy

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## ABSTRACT

**Nonmyeloablative allogeneic transplantation provides a valuable therapeutic option for patients with relapsed non-Hodgkin lymphomas, particularly those that have recurred after autologous transplantation. However, the absence of an intensive conditioning regimen renders this approach less effective for patients with aggressive or bulky lymphoma because rapid tumor growth may outpace the evolution of the graft-versus-lymphoma effect. Radioimmunotherapy provides an attractive, minimally toxic modality to safely prevent early progression of B-cell lymphomas and induce remissions without incurring the risks of traditional intensive therapy. This approach provides a time window during which a robust graft-versus-lymphoma effect may be established before tumor progression, thereby providing more effective long-term disease control. The rationale for incorporation of radioimmunotherapy into reduced intensity allogeneic transplantation regimens for non-Hodgkin lymphoma is discussed, as are current study designs, preliminary results, and future directions.**


## KEY WORDS

Radioimmunotherapy • Allogeneic • Non-myeloablative • Lymphoma • CD20

## INTRODUCTION

The curative potential of conventional allogeneic hematopoietic cell transplantation (HCT) is due in part to eradication of the malignant cell by high-dose chemoradiation therapy and in part by immune-mediated graft-versus-tumor effects [1]. Unfortunately, high-dose myeloablative regimens are associated with serious toxicities that have limited their use to younger, medically fit patients despite the fact that the highest incidence of non-Hodgkin lymphoma (NHL) occurs in adults >60 years of age [2]. Nonmyeloablative allogeneic HCT has recently been introduced as a novel, potentially curative option for patients with relapsed or refractory NHL that can overcome some the limitations of traditional myeloablative therapies [3-8]. This approach is particularly attractive for patients who are not candidates for myeloablative autologous transplantation due to the inability to collect autologous stem cells or the presence of excessive comorbidities, or patients who are unable to undergo traditional myeloablative allogeneic HCT as a result of prior autologous transplantation, excessive comorbidities, or advanced age. Allogeneic HCT also may be more likely to cure patients with indolent lymphomas than autologous transplantation, although the routine application of this approach has been limited by the high mortality rates of conventional myeloablative allografting [9,10]. The attractiveness of nonablative allogeneic HCT emanates predominantly from its favorable toxicity profile [3,11]. The reduced intensity of the employed conditioning regimens markedly attenuates early morbidity and mortality rates. However, this same attribute enhances the risk of early relapse because disease control is almost entirely

**Table 1.** *Selected Trials of Nonablative Allogeneic HCT for Lymphoma and Disease Status Before Transplantation**

| Study | n | Histology | Chemosensitive†, n (%) | CR, n (%) | ≥5 cm Bulk (%) | PFS |
|---|---|---|---|---|---|---|
| Khouri et al [3] | 20 | FL/SLL | 20 (100) | 12 (60) | NA | 84% at 2 y |
| Maris et al [4] | 33 | MCL | 18 (55) | 13 (39) | 6 (18) | 60% at 2 y |
| Sorror et al [5] | 64 | CLL/SLL | 23 (36) | 5 (8) | 18 (28) | 52% at 2 y |
| Morris et al [6] | 88 | Various | 78 (89) | 21 (24) | NA | 30–49% at 3 y |
| Corradini et al [7] | 17 | T-NHL | 14 (82) | 2 (12) | NA | 64% at 3 y |
| Dean et al [8] | 29 | Various | 12 (41) | 3 (10) | NA | 32% at 3 y |
| Robinson et al [13] | 188 | Various | 133 (71) | 49 (26) | NA | 46% at 1 y |

*FL indicates follicular lymphoma; SLL, small lymphocytic lymphoma; MCL, mantle cell lymphoma; CLL, chronic lymphocytic leukemia; T-NHL, T-cell non-Hodgkin's lymphoma; CR, complete remission; NA, not available; PFS, profession-free survival.
†A partial or complete response to the most recent therapy before transplantation.

reliant on the graft-versus-lymphoma effect, which requires 30 to 60 days to develop [12]. This article reviews the potential limitations of nonablative allogeneic HCT for NHL in terms of early disease control and summarizes the rationale and methods of incorporating radioimmunotherapy (RIT) into reduced intensity conditioning regimens.

## SUCCESS AND LIMITATIONS OF NONABLATIVE ALLOGENEIC HCT FOR NHL

Several centers have published pilot data regarding the efficacy of reduced intensity conditioning regimens for NHL. Selected studies of nonablative allogeneic HCT for lymphoma are summarized in Table 1. Khouri and colleagues [3] of the MD Anderson Cancer Center published one of the earliest studies of nonablative allogeneic HCT for indolent lymphoma, using a moderately intensive preparative regimen consisting of 5 days of fludarabine with 1 g/m$^2$ of cyclophosphamide. In this series of 20 patients with relapsed or refractory lymphoma (predominantly follicular lymphoma), 84% were estimated to be alive and without progression 2 years after HCT. However, only patients with chemosensitive disease were included in this trial; most had responded to cyclophosphamide and/or fludarabine-based regimens, and 60% were in complete remission before transplantation.

In a second study, Maris and coworkers [4] evaluated the efficacy of a low-intensity allogeneic conditioning regimen consisting of 3 days of fludarabine with 2-Gy total body irradiation in patients with relapsed or refractory mantle cell lymphoma. In this series of 33 patients, 42% had failed high-dose autologous transplantation and 39% were refractory to their last therapy. Despite these features, 60% of patients were estimated to be alive and without progression after 2 years. A significant association was observed between relapse and the receipt of ≥4 prior regimens in this study ($P = .01$).

Morris and colleagues [6] formally evaluated the risk factors for post-transplantation relapse in a multivariable analysis of 88 patients with NHL undergoing nonablative allogeneic HCT. Their findings suggested that failure to achieve a complete remission before transplantation exerted the greatest adverse effect on the risk of relapse after transplantation (relative risk, 3.3; $P = .0001$) [6]. Concordant results emerged from a second series of 188 patients with NHL who were treated with nonablative allogeneic HCT, which identified response to chemotherapy as the only significant independent predictor of relapse, with 75% of patients with chemotherapy-resistant lymphoma progressing within 1 year after transplantation compared with 25% of patients with chemotherapy-sensitive disease ($P = .001$) [13]. Unpublished data from our center that evaluated 64 patients with chronic lymphocytic leukemia/small lymphocytic lymphoma who underwent reduced intensity allogeneic HCT confirmed these findings (Figure 1) and demonstrated a 2-year relapse rate of 52% in patients with tumor masses >5 cm in diameter at time of transplantation compared with 14% for patients with tumors ≤5 cm ($P = .009$; Sorror et al, unpublished data). Together, these studies suggest that nonablative allogeneic HCT has encouraging efficacy for treatment of NHL, but that results are inferior for patients

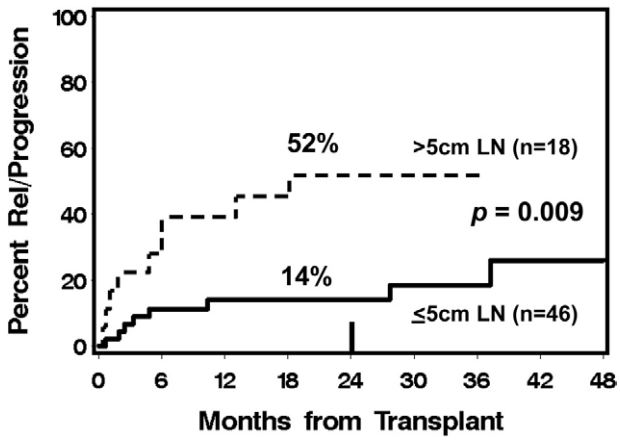


**Figure 1.** Effect of tumor bulk on the cumulative incidence of relapse after nonablative allogeneic HCT for chronic lymphocytic leukemia/small lymphocytic lymphoma (Sorror et al, unpublished data). LN indicates lymph node.

**Table 2.** *Properties of Food and Drug Administration Approved Radioimmunoconjugates Yttrium-90-Ibritumomab-Tiuxetan (Zevalin; Biogen-Idec) and Iodine-131-Tositumomab (Bexxar; GlaxoSmithKline)*

| | Yttrium 90-Ibritumomab-Tiuxetan | Iodine-131-Tositumomab |
|---|---|---|
| **Antibodies** | | |
| Labeled antibody | Ibritumomab tiuxetan (murine) | Tositumomab (murine) |
| Unlabeled antibody | Rituximab (chimeric) | Tositumomab (murine) |
| **Target** | CD20 | CD20 |
| **Isotopes** | | |
| Therapeutic isotope | Yttrium 90 | Iodine 131 |
| Emission | β | β, γ |
| Beta energy | 2.3 MeV | 0.6 MeV |
| Pathlength | ~5 mm | ~1 mm |
| Isotope halflife* | 2.7 d | 8 d |
| Imaging isotope | Indium 111 | Iodine 131 |
| Nonspecific uptake | Bone, liver | Thyroid† |
| Dose calculation‡ | 0.4 mCi/kg (up to 32 mCi) | 75 cGy whole-body dose§ |

*The in vivo biological half-time may be shorter due to clearance of the radioimmunoconjugate.
†Thyroid uptake can be blocked with oral Lugol solution or super-saturated potassium iodide solution.
‡Dose reduction required for platelet counts <150 000/μL.
§The millicurie dose is variable based on individual dosimetry to deliver the desired whole-body radiation dose.

with bulky, chemoresistant, or residual disease at time of transplantation.

## RIT FOR TREATMENT OF NHL

RIT has recently emerged as one of the most promising modalities for the treatment of NHL. Two drugs have been approved by the US Food and Drug Administration for treatment of relapsed or refractory follicular and transformed follicular NHL, namely iodine-131-tositumomab (Bexxar, GlaxoSmithKline, Philadelphia, PA) and yttrium 90-ibritumomab-tiuxetan (Zevalin, Biogen-Idec, Cambridge, MA). The properties and features of these agents are summarized in Table 2. Objective response rates of 60% to 80% have been reported in multiple trials [14-17]. More recently, data have suggested that RIT also is effective for treatment of more aggressive histologies including diffuse large B-cell lymphoma and mantle cell lymphoma [18,19]. Because myelosuppression is the major dose-limiting toxicity of RIT, HCT may be the ideal setting for this modality. Furthermore, patients with NHL who undergo nonablative allogeneic HCT and are heavily pretreated with chemotherapy may be less cross-resistant to the use of radiation therapy than to the use of additional chemotherapy. Our group and others have used RIT at standard or high doses as part of a high-dose therapy regimen in the setting of autologous transplantation and have shown this approach to be feasible, efficacious, and safe, without a negative effect on engraftment [20-26]. Thus, RIT may provide an optimal strategy for reduced intensity allogeneic transplantation conditioning by inducing an effective antitumor response with minimal nonhematologic toxicity. This principle has been validated by our group in the setting of allogeneic HCT for acute leukemia, using CD45 targeted RIT, which has been shown to be feasible and effective in patients with relapsed acute myeloid leukemia [27-29].

## OPTIMIZING CONDITIONING REGIMENS CONTAINING RIT

Johnson and Press [30] evaluated a variety of drugs for their ability to synergize with iodine 131–based anti-CD20 RIT in an in vitro lymphoma model to define optimal combinations for transplantation conditioning regimens. These studies employed formal isobolographic and dose modification factor analyses to demonstrate that nucleoside analogs such as cytarabine and fludarabine synergize optimally with RIT, whereas agents traditionally used in lymphoma transplantation regimens such as cyclophosphamide and etoposide provided minimal synergy (Figure 2). Subsequent in vivo murine lymphoma xenograft studies have suggested that combinations of fludarabine and

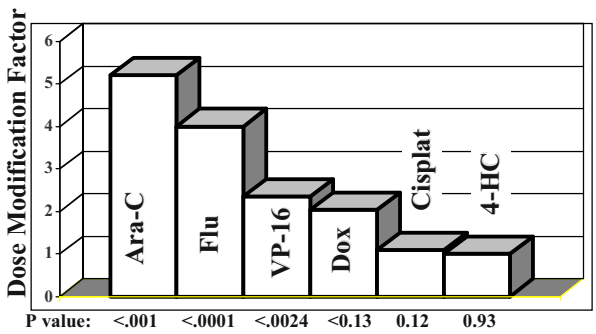


**Figure 2.** In vitro degree of synergy between iodine 131/anti-CD20 RIT and chemotherapeutic agents (adapted from Johnson and Press [30]). Ara-C indicates cytarabine; Flu, fludarabine; VP-16, etoposide; Dox, doxorubicin; Cisplat, cisplatin; 4-HC, 4-hydroxycyclophosphamide.

iodine 131 anti-CD20 antibodies improve survival of mice bearing human lymphoma xenografts (Figure 3; Gopal et al, unpublished data). These findings, in concert with knowledge of the effective T-cell ablation provided by fludarabine, has convinced our group to combine RIT with concurrent fludarabine as part of the reduced intensity transplantation conditioning regimen for lymphoma patients with substantial tumor bulk.

## CURRENT STUDIES OF RIT-BASED ALLOTRANSPLANTS FOR NHL

Our interest in developing a formal RIT-based reduced intensity transplantation protocol was heightened by early experiences of individual patients treated with standard doses of Bexxar or Zevalin shortly before undergoing standard nonablative allogeneic HCT. Encouraging outcomes in such patients convinced us to initiate formal studies using RIT as part of reduced intensity allogeneic transplantation conditioning at our center. The current study approved by the institutional review board uses yttrium-90-ibritumomab tiuxetan at the standard dose (.4 mCi/kg) combined with fludarabine (30 mg/m$^2$ × 3 days), total body irradiation (2 Gy on day 0), and immunosuppression with cyclosporine and mycophenolate mofetil starting on day −3 and day 0, respectively (Figure 4). One notable deviation from our traditional nonablative allogeneic HCT conditioning regimen is that fludarabine is administered on day −7 rather than on day −3 to overlap more extensively with RIT and provide a greater opportunity for synergy between these 2 agents [4]. This study permits accrual of patients who have received prior autologous transplants, have had prior dose limiting radiation, and have progressive, bulky, or chemoresistant disease and has safety as its primary endpoint. We anticipate that this trial will capture patients who have too great a disease burden for traditional reduced intensity allogeneic transplantation and those who are too old, have had too many prior therapies, or possess too many significant comorbidities to undergo traditional myeloablative allogeneic transplantation. Six patients have provided written informed consent and been enrolled in this ytttrium-90-ibritumomab–based allogeneic transplantation study to date. None of the evaluable patients have shown disease progression and 3 achieved an objective response by 1 month after transplantation, even though all patients had chemoresistant lymphoma and a mean tumor bulk of 6.5 cm at the time of study entry.

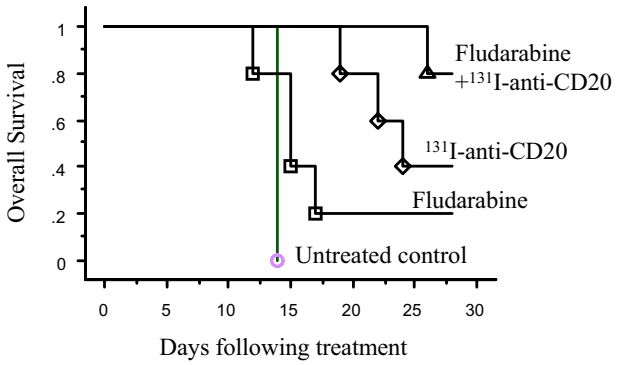


**Figure 3.** Overall survival of mice bearing human lymphoma xenografts treated with iodine-131-tositumomab ($^{131}$I-anti-CD20), fludarabine, iodine-131-tositumomab + fludarabine, or diluent alone (control). (From Gopal et al, unpublished data.)

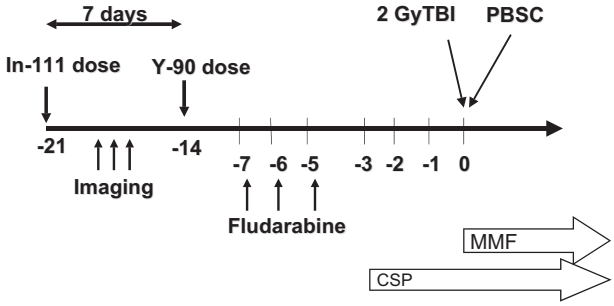


**Figure 4.** Schema of yttrium 90 (Y-90)/anti-CD20 RIT conditioning. CSP indicates cyclosporine; MMF, mycophenolate mofetil; PBSC, allogeneic peripheral blood stem cell transplantation; TBI, total body irradiation.

## FUTURE DIRECTIONS IN RIT-BASED ALLOTRANSPLANTS FOR NHL

We anticipate that standard RIT alone will not be sufficient to control lymphoma in all patients with very rapidly progressive or excessively bulky disease. To overcome this clinical challenge, we anticipate that future studies will require escalation of the radiation dose delivered to tumor sites. One approach is to mirror the regimens we have employed in our autologous NHL transplantation and allogeneic acute myeloid leukemia transplantation regimens by escalating the dose of radiation delivered by RIT [20,21,27]. Other strategies include targeting radiation more selectively to tumor sites using pretargeting methodologies or extracorporeal immunoabsorption [31-34]. Based on these considerations, we anticipate that the use of RIT will help overcome the limitations of reduced intensity allogeneic HCT in patients with chemoresistant, bulky, or rapidly progressive lymphoid malignancies. We encourage continued development and accrual to clinical trials so that the safety and efficacy of these approaches can be most properly evaluated.

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